CLAIM OBJECTIONS

Claims 8-14, 20-21, 23-25 are objected to under 37 CFR 1.75(c) as being in improper form due to improper multiple dependency. Claims 8-14, 20-21, 23-25 have been amended to eliminate the multiple dependency of the claims. Applicants respectfully submit that the rejection is moot and should be withdrawn.

REJECTIONS UNDER 35 USC §112, SECOND PARAGRAPH

Claims 1-7, 15-19, 22, 26-28 are rejected under 35 USC §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. Specifically, the Examiner states that the claims are indefinite because the diameter of the micronized particles may include a diameter of zero. Pursuant to the Examiner's suggestions, independent claims 1 and 15 have been amended to indicate a lower range for the particle size. Accordingly, it is respectfully submitted that any indefiniteness has been eliminated and that the rejections to claims 1-7, 15-19, 22, 26-28 should be withdrawn.

REJECTIONS UNDER 35 USC §103(A)

Claims 1-7, 15-19, 22, and 26-28 are rejected under 35 USC § 103(a) as being unpatentable over Clark (USP 5,641,510) in view of Rose ("Evaluation of Sodium colistimethate Aerosol") and Catchpole ("A re-assessment of in-vitro activity of Colistin SMS"). The Examiner asserts that the claims of the present invention are obvious because one of ordinary skill in the art would have modified the composition taught by Clark and substituted colistin sulphomethate sodium as taught by Rose and Catchpole.

Applicants respectfully submit that Clark in view of Rose and Catchpole does not render the present invention obvious because a *prima facie* case of obviousness has not been established. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The

teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The initial burden is on the Examiner to provide some suggestion of the desirability of doing what is the inventor has done. "To support the conclusion the claimed invention is directed to obvious subject matter, either the references expressly or implicitly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why an artisan would have found the claimed invention to have been obvious in light of the teachings of the references." Ex parte Clapp, 227 USPQ 972, 973 (Bd. Pat. App.& Inter. 1985).

Applicants respectfully assert that the prima facie case of obviousness has not been met as the cited prior art references do not teach all the limitations of as recited in the claims of the present invention. More specifically, neither Clark, Rose nor Catchpole teach micronized powder particles of colistin SMS. Rather, Clark teaches that pharmaceutical powders may be included within a capsule treated with a lubricant. Moreover, neither the Rose nor Catchpole references teach the delivery method of colistin SMS. Accordingly, at the time the Catchpole and Rose articles were written, a person of ordinary skill in the art would generally understand (as discussed in the introduction to the present application) that Colistin SMS is administered through a nebulizer in liquid droplet form. More specifically, Rose discusses a colistimethate powder for reconstitution. Although the powder "as is" is substantially free from water, the intended use is for dissolution in water or saline solution and then the administration of this solution as a nebulized aerosol into the lungs. The commercial product described by Rose contains thiomersol, dibucaine and citrate buffer. A person of ordinary skill in the art would understand that these are not carriers as such and would certainly not aid delivery into the lungs as thiomersol is a preservative, dibucaine is a local anaesthetic and citrate buffer is used for modification of the pH of the solution. There is no discussion or indication that sodium colistimethate could be used in micronized powder form. Accordingly, because these prior art references fail to teach

all the limitations of claims of the present invention, Applicants respectfully submit that claims 1-7, 15-19, 22, and 26-28 are allowable.

Furthermore, a person of ordinary skill in the art would not have a reasonable expectation of success when combining the teachings of Clark, Catchpole, and Rose. First, Clark does not teach or suggest that the drugs disclosed in Clark may be readily substituted with colistin SMS. That is, those skilled in the art would appreciate that colistin SMS has vastly different drug loading characteristics as compared to the drugs disclosed in Clark. More specifically, Colistin SMS a very high loading of drug is required (approximately 125 milligrams) whereas the drugs disclosed in Clark (See Table 2) are delivered in sub-milligram quantities. For Colistin SMS, the amount of powder which would be retained in the capsule is a very low percentage, due to the very high amount of powder which is in the capsule itself. Therefore, Clark can only be seen as being a general description of the use of micronized powders in inhalation therapy with no description (either in general of specific terms) to Colistin SMS.

Additionally, taking the disclosure of Clark, Catchpole and Rose, one of ordinary skill in the art would not arrive at the subject matter of the present invention. The teaching of Rose and Catchpole would indicate the use of liquid aerosol administration of Colistin SMS. However, studies of aerosol administration have shown that only one percent of the aerosol mass leaves the nebulizer directly. The outgoing air becomes saturated with water derived from liquid retained in the nebulizer and this has two important consequences: firstly, the nebulizer is cooled and reaches an equilibrium temperature approximately 10°C below ambient, so that the patient inhales a relatively cold spray while secondly the evaporation of water causes the concentration of solutes to increase with time. This is a problem when trying to deliver a relatively high dosage of drug. The nebulizers themselves which are used by patients have to be bulky due to the air compressors which are required and are not truly portable in the same way as a hand-held inhaler. The Applicants have found that Colistin SMS can be delivered in micronized dry powder form using a commercially available hand-held inhaler. This is clearly not taught in the prior art. There is no indication to one of ordinary skill in the art that the composition of Clark could be substituted by Colistin SMS as taught by Rose

and Catchpole, mainly for the reason that the latter pieces of prior art discuss liquid systems.

Accordingly, Applicants respectfully submit that the claims of the present invention are patentable over the cited prior art references and request allowance of the presently pending claims.

CONCLUSION

In view of the above remarks and amendments, it is submitted that the pending claims are in condition for allowance and their allowance is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**."

If any issues remain, the Examiner is urged to contact the undersigned by telephone for a prompt resolution thereof.

No additional fees are seen as being necessary in connection for this amendment. However, the Examiner is authorized to charge any additional fees or credit any overpayment to Deposit Account 50-1901.

Respectfully submitted,

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Louis C. Cullman
Registration No. 39,645

OPPENHEIMER WOLFF & DONNELLY LLP
840 Newport Center Drive, Suite 700
Newport Beach, CA 92660
Telephone: 949.823.6000
Facsimile: 949.823.6100

4:5:30

Version with markings to show changes made

[0002] The present application relates to improvements in or relating to pharmaceutical compositions comprising [micronised] micronized colistin sulphomethate sodium.

[0016] It has now been discovered that [micronised] micronized colistin sulphomethate sodium can be administered to the airways of a patient using a powder dose inhalation device. The [micronised] micronized colistin may be used alone or with a carrier, such as lactose.

[0017] According to the present invention, there is firstly provided the use of [micronised] micronized colistin sulphomethate sodium in a method of treatment of the human body, particularly in the treatment of bacterial infections of the pulmonary system, most particularly in the treatment of secondary infections in patients suffering from cystic fibrosis, by powder inhalation.

[0018] According to a further aspect of the present application, there is provided a pharmaceutical composition comprising [micronised] micronized colistin sulphomethate sodium and a carrier, in the absence of free liquid.

[0019] According to a yet further aspect of the present invention, there is provided a pharmaceutical dosage form suitable for use with a dry powder inhaler comprising [micronised] micronized colistin sulphomethate sodium, optionally together with a carrier, and a container. The container is preferably a capsule.

[0020] Figure 1 shows a particle size analysis of [micronised] micronized colistin sulphomethate sodium.

In the claims:

Please cancel claims 22, 26, 27 and 28.

Please amend claims 1, 2, 4, 6-13, 15, 18-21, 23, and 25 as follows:

1. Micronized powder [Micronised] particles of colistin sulphomethate sodium wherein at least 90% by volume of the [micronised] micronized particles have a diameter of [less than] from 0.01 to 10 micrometers for use in the treatment of a

pulmonary infection by powder inhalation, wherein the colistin sulphomethate sodium is not separated into component form.

2. Colistin sulphomethate sodium for the use as claimed in Claim 1 wherein the [micronised] micronized powder is mixed with a carrier.

4. A composition comprising [micronised] micronized colistin sulphomethate sodium as defined in Claim 1 and a carrier, in the absence of free liquid.

6. A composition as claimed in Claim 4 [or Claim 5] wherein the ratio of colistin sulphomethate sodium to carrier is from 5:1 to 1:2 by weight.

7. A composition as claimed in Claim 4 [or Claim 5] wherein the ratio of colistin sulphomethate sodium to carrier is from 4:1 to 1:1 by weight.

8. The composition as claimed in [any one of Claim[s] 4 [to 7] wherein at least 50% by volume of the carrier particles have an effective particle size in the range of 30-150 micrometers.

9. A composition as claimed in [any one of] Claim[s] 4 [to 8] wherein at least 50% by volume of the [micronised] micronized colistin sulphomethate sodium has a particle diameter of [less than] from 0.01 to 8 micrometers.

10. A composition as claimed in [any one of] Claim[s] 4 [to 9] wherein at least 25% of the particles of [micronised] micronized colistin sulphomethate sodium have a diameter of [less than] from 0.01 to 6 micrometers.

11. A composition as claimed in [any one of] Claim[s] 4 [to 10] wherein the [micronised] micronized colistin sulphomethate sodium is prepared in the desired particle size range using a fluid energy mill.

12. A process for the preparation of a composition as claimed in [any one of] Claim[s] 4 [to 11] which comprises mixing [micronised] micronized colistin sulphomethate sodium and a carrier.

13. A pharmaceutical dosage form suitable for use with a dry powder inhaler comprising [micronised] micronized powdered colistin sulphomethate sodium wherein at least 90% by volume of the particles have a diameter less than 10 micrometers or a composition according to any [one of] Claim[s] 4 [to 11] and a container, said dosage having a content of below 10 wt % water.

15. A capsule containing [micronised] micronized colistin sulphomethate sodium wherein at least 90% by volume of the [micronised] micronized powdered particles have a diameter of [less than] from 0.01 to 10 micrometers.

18. A capsule as claimed in [any one of] Claim[s] 15 [to 17] further comprising a carrier.

19. A capsule as claimed in Claim [18] 15 when the carrier is lactose.

20. A capsule according to [any one of] Claim[s] 15 [to 19] which is opaque.

21. A capsule according to [any one of] Claim[s] 15 [to 19 or a composition according to any one of Claims 4 to 11] packed in an opaque container.

23. A capsule according to [any one of] Claim[s] 15 [to 22] which additionally comprises a [micronised] micronized bronchodilatory drug.

25. A capsule according to Claim 23 [or Claim 24] which comprises from 50 to 150 milligrams of colistin sulphomethate sodium and from 1 to 250 micrograms of bronchodilatory drug.

Please add new claim 29 as follows:

29. (New) A composition according to Claim 4 packed in an opaque container.